Asian Journal of Surgery (2015) 38, 40–46

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-asianjournalsurgery.com

BRIEF COMMUNICATION

# A clinical series and literature review of the management of inguinal nodal metastases in patients with primary extramammary Paget disease of the scrotum

Ye Xin Koh [a], Timothy Kwang Yong Tay [b], Sheng Xu [a], Chee Meng Lee [a], Melissa Ching Ching Teo [a,*]

[a] *Department of Surgical Oncology, National Cancer Centre, Singapore*
[b] *Department of Pathology, Singapore General Hospital, Singapore*

Received 1 May 2014; received in revised form 13 August 2014; accepted 15 August 2014
Available online 16 October 2014

**KEYWORDS**
cloquet node;
extramammary paget disease;
inguinal lymphadenectomy

**Summary** We describe a series of five patients with extramammary Paget disease of the scrotum with inguinal nodal metastases. These patients underwent combined groin dissection. All patients experienced invasion to the dermis. One patient had invasion of the dartos muscle, another had tumor invading into the skeletal muscle and femoral vein. Four patients had positive Cloquet node involvement on frozen section and formal histology, but only one patient had positive pelvic nodal disease. Another patient with pelvic nodal metastases seen on computed tomography scan had no Cloquet node identified intraoperatively but had positive pelvic nodal metastases. The mean disease-free survival and the overall survival were 28.6 months (range: 2–60 months) and 33.4 months (range: 2–60 months), respectively, for all patients. Three patients developed distant metastases and two patients were disease free to date. No locoregional recurrences were observed. Aggressive lymphadenectomy in selected cases can provide a long-term survival benefit. The use of Cloquet node in the prediction of pelvic nodal disease should be considered. Based on the literature review, sentinel lymph node biopsy can potentially diagnose occult metastases in otherwise nonenlarged nodes.


Conflicts of interest: The authors have no conflicts of interest to declare.

* Corresponding author. Senior Consultant, Department of Surgical Oncology, National Cancer Centre Singapore, 11 Hospital Drive, Singapore 169610.
*E-mail address:* melissa.teo.c.c@nccs.com.sg (M.C.C. Teo).

http://dx.doi.org/10.1016/j.asjsur.2014.08.001

## 1. Introduction

Extramammary Paget disease (EMPD) is a distinct form of rare malignant skin neoplasm first described by Radcliffe Crocker in 1889.[1] EMPD is known to affect primarily postmenopausal Caucasian females with a female-to-male ratio of 4:1.[2–4] The lesions commonly develop in the vulva, penis, scrotum, perineum, perianal area, umbilicus, or axilla.[5] Primary EMPD arises from underlying neoplastic transformation of basal epithelial cells of the epidermis or the epithelial cells in the intraepidermal portion of sweat glands. By contrast, the secondary form of EMPD is caused by intraepidermal spreading of neoplastic cells typically from an underlying adenocarcinoma.[6,7]

EMPD lesions are generally confined to the epidermis. However, as the disease progresses, EMPD is known to invade the dermis and metastasize to regional lymph nodes or distant organs.[8] Wide excision is currently the treatment of choice for early EMPD, whereas lymph node dissection is only performed when nodal metastases are present. Compared with patients with carcinoma *in situ*, patients with EMPD invading beyond the dermis or subcutaneous tissues or regional lymph node metastasis appear to have a much worse prognosis.[9,10] The 5-year survival rate of patients with lymph node metastasis is extremely poor. In a retrospective analysis of 34 patients with genital EMPD in the study by Tsutsumida et al,[11], no patients with nodal metastases survived >50 months. By contrast, the remaining patients without lymph node metastases had a cumulative survival of >5 years. In the study by Ito et al,[12] the 5-year survival rate of patients with genital EMPD and nodal metastases was 20%, compared to 87.4% in patients without nodal metastases.

The published series of EMPD described lymphadenectomy for the treatment of inguinal nodal metastases but did not describe the more extensive combined groin dissection (CGD) more commonly performed for inguinal and pelvic nodal metastases in malignant melanoma.[11–13] In a study reported by Karouski et al,[14] favorable 10-year survival rates of 25% have been observed in melanoma patients with nodal disease who underwent CGD.

In this study, we describe our experience in the management of five male patients with advanced primary EMPD of the scrotum and palpable inguinal nodal metastases from a total of 14 patients with EMPD treated at the Singapore National Cancer Centre, Singapore between January 2002 and January 2012. In addition, we performed a literature review of published studies describing the management of nodal metastases in individuals with genitalia EMPD.

## 2. Materials and methods

The SingHealth Institute Ethics Board-approved retrospective analysis examines a prospectively maintained database of 14 EMPD patients treated at the Singapore National Cancer Centre, a tertiary referral center, between the 11-year period of January 2002 to January 2012. Five patients with inguinal nodal involvement who underwent CGD were reviewed.

The medical records of these patients were obtained from a prospectively maintained computerized clinical database (Sunrise Clinical Manager version 5.8, Eclipsys Corporation, Atlanta, Georgia). Surgical findings and surgical procedures were also obtained from another prospectively maintained computerized operative database (OTM 10, IBM, Armonk, New York). These patients had been evaluated by routine history and physical examination, chest radiography, and blood profiles at the time of presentation. Imaging studies using computed tomography (CT) or magnetic resonance imaging (MRI) were also performed to evaluate locoregional disease. All the biopsy results and preoperative imaging scans were reviewed prior to surgical treatment by a multidisciplinary tumor board to assess the extent of local disease and lymph node involvement. All of the patients subsequently underwent surgery within 1 month after diagnosis.

All patients underwent wide resection of the lesion until the frozen sections of the margins were negative. Superficial groin dissection (SGD) was defined as the complete dissection of lymph nodes from the inguinofemoral content to the apex of the femoral triangle. CGD further included dissection of the external iliac nodes up to at least the bifurcation of the common iliac artery and dissection of the obturator nodes. Consideration was made for CGD if the preoperative CT/MRI studies showed significantly enlarged lymph nodes along the iliac vessels or when the frozen section of the Cloquet node was positive for disease. Lymph nodes were considered significantly enlarged if they were >1 cm on CT/MRI. The Cloquet node was defined as the lymphatic tissue medial to the femoral vein at the superior aspect of the femoral canal and is thought to represent the leading lymph node into the pelvis from the inguinal basin. Reconstruction was performed primarily with a sartorius flap to cover the femoral vessels. Closed suction drains were placed in the area of the groin dissection.

The resected primary lesion and dissected lymph nodes were sent for histological examination. The epidermis showed tumor cells with large atypical nuclei and abundant cytoplasm, arranged singly and in small groups. Histochemical stains and immunohistochemical stains had been used, when necessary, to confirm the glandular nature of these cells and to rule out the possibility of a secondary EMPD. The resection margins, depth of invasion, and presence of nodal metastasis were assessed. The histological slides were reviewed specifically for the presence of invasion into the dermis, subcutaneous tissue, smooth muscle of the scrotum (dartos muscle), regional skeletal muscles, or blood vessels. The number and the level of inguinal and iliac node involvement by metastasis, with or without the presence of extranodal spread, were also recorded.

Patients were then followed up every 3–6 months after surgery. Surveillance biopsies and imaging studies were not routinely performed in asymptomatic patients. Clinical investigations were performed according to the patient's symptoms at follow-up.

## 3. Results

Scrotal primary EMPDs were diagnosed in five Asian males, mean age 62.5 years (range: 43–77 years). All patients underwent scrotal incision or punch biopsies, which suggested EMPD of the scrotum. Fine-needle aspiration

cytology of the inguinal lymph nodes was performed in three patients, and only one had positive results. Imaging studies suggested involvement of the pelvic nodes in three patients; histology confirmed involvement in two of them. Two patients developed wound infection and lymphedema after CGD (Table 1).

All patients had invasion to the dermis and one patient had invasion to the dartos muscle; another had tumor invading into the skeletal muscle and femoral vein. All radial skin margins were negative; the closest margin was 4 mm. Of the four patients who had positive Cloquet node involvement on frozen section and formal histology, one had pelvic nodal disease. In another patient with pelvic nodal metastases seen on CT scan, the Cloquet node was not identified intraoperatively but positive pelvic nodal metastases were present (Table 2).

The mean disease-free survival (DFS) and the overall survival (OS) were 28.6 months (range: 2–60 months) and 33.4 months (range: 2–60 months), respectively, for all patients. Three patients developed distant metastases and two patients were disease free.

## 4. Discussion

Geital EMPD is rare and most studies have limited numbers ($n < 50$) in most published series. From our review, there were 205 cases of genital EMPD reported from six case series worldwide, of which 47.3% ($n = 97$) of them had invasive disease. Genital EMPD with inguinal nodal metastases accounts for 35.1% of all invasive genital EMPD and 16.5% of all genital EMPD cases. Of those with invasive EMPD, only 37.1% ($n = 36$) underwent SGD and 34 of 36 had evidence of inguinal nodal metastases on dissection.[11–13,15–18]

There is currently no universally accepted approach to the management of inguinal and pelvic nodal disease in these EMPD patients. The available evidence in the management of this disease is presented in Table 3.

Achieving adequate margins for the primary skin lesions is an important factor in reducing the risk of recurrent disease. It was suggested that the critical factor in the management of the primary skin lesions was the vertical invasion at the local region, and that a wide excision margin of 2–5 cm for the primary genital lesion was recommended.[11,19] In our series, the radial and vertical margins were aggressively pursued; consequently, no patient developed locoregional recurrence.

The depth of the primary lesion of the EMPD has also been thought to influence the development of nodal metastases and overall survival; several studies have reported that all patients with only intraepidermal disease did not develop nodal metastases. Furthermore, the survival of these patients was significantly better than those with invasive disease, median survival of 55 months versus 14.5 months.[13,17]

Tsutsumida et al[11] proposed an algorithm for lymph node dissection according to the depth of invasion of the primary lesion. When invasion to the dermis or subcutaneous tissue is found, elective lymph node dissection is strongly recommended even in the absence of clinically palpable inguinal nodes. In this study, survival was adversely affected by the depth of tumor invasion. When the tumor

**Table 1** Clinical, pathological, and radiological characteristics of primary scrotal extramammary Paget disease with groin nodal metastases.

| Patient no. | Age/sex | Location | Diagnostic delay (mo) | Size of scrotal lesions (mm) | Ulcer | Depth of invasion | FNAC of inguinal node | CT scan enlargement of pelvic nodes | Cloquet node status (frozen section/final histology) | Pathological status of pelvic node | Reconstruction | Postoperative complications |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 43/male | left scrotum | 12 | 20 | Yes | Dermis | Non-conclusive | Yes | Positive/positive | Negative | Sartorius flap | Seroma |
| 2 | 55/male | left scrotum and medial thigh | 24 | 100 | Yes | Skeletal muscle, femoral vein | positive | Yes | Positive/positive | Positive | Sartorius flap and fasciocutaneous tensor facia lata flap and split skin graft from the right thigh. | Superficial wound infection Flap necrosis, lymphedema |
| 3 | 71/male | left scrotum | 6 | 30 | Yes | Dartos muscle | Negative | No | Positive/positive | Negative | Sartorius flap | Nil |
| 4 | 77/male | left scrotum | 12 | 20 | No | Dermis | Not done | No | Positive/positive | Negative | Sartorius flap | Nil |
| 5 | 67/male | left scrotum | 36 | 20 | No | Dermis | Not done | Yes | Fibrofatty tissue only, no LN seen | Positive | Sartorius flap | Superficial wound infection, lymphedema |

CT = computed tomography; FNAC = fine-needle aspiration cytology.

**Table 2** Pathological factors in relation to disease-free survival and overall survival.

| Patient no. | Radial margins of scrotal lesion (mm) | Deep margins of scrotal lesion | Depth of primary EMPD invasion | No. of lymph nodes involved | Pathological status of pelvic node | Largest lymph node size (mm) | Extranodal spread | Disease-free survival (mo) | Overall survival (mo) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 10 | Negative | Deep dermis | 12/13 | Negative | 20 | No | 46 (lung metastases) | 48 |
| 2 | 4 | Positive | Skeletal muscle, femoral vein | 42/42 | Positive | 35 | Yes | 2 (bone metastases) | 2 |
| 3 | 10 | Negative | Dartos muscle | 8/9 | Negative | 35 | Yes | 6 | 6 |
| 4 | 20 | Negative | Deep dermis | 2/13 | Negative | 10 | No | 60 | 60 |
| 5 | 17 | Negative | Deep dermis | 8/34 | Positive | 35 | No | 29 (cervical node and peritoneal metastases) | 51 |

EMPD = extramammary Paget disease.

extended into the dermis, 50% of the patients (3 of 6) were found to have nodal metastases; the median survival was 54 months with no 5-year survivors. When the tumor extended deeper to the subcutaneous tissue, all six patients had lymph node metastasis; the median survival was 24 months and likewise there were no 5-year survivors.[11] Similarly, Ito et al[12] showed an inferior 5-year survival rate of D patients with EMPD and positive nodal involvement versus negative nodal involvement (20% vs. 87.4%).[12] In another study by Yoshino et al,[20] the number of nodes involved was a crucial determinant of survival. In patients with more than a single positive node, the 5-year survival rate was only 13.5% compared to 100% in patients with only single node involvement.

This poor survival was not observed in our case series. There were three patients with dermal invasion and multiple involved nodes who underwent combined groin dissection and enjoyed relatively long survival (4–5 years; Table 2). Furthermore, all the patients in our series did not develop recurrent locoregional disease. At our center, CGD is guided by the intraoperative frozen section results of the Cloquet node and imaging investigations are also taken into consideration. The Cloquet node has been identified to reflect the status of the pelvic nodes in the treatment of melanomas with groin nodal metastases, the positive predictive value of a positive Cloquet node was >67%.[21–23] Although the positive predictive value of the Cloquet node for EMPD in our series was much lower, the removal of the involved Cloquet node was important in ensuring complete lymphadenectomy.

According to our results, muscle and vascular invasion were very poor prognostic indicators. In the patient with these factors, metastatic disease developed 2 months after the surgery; the patient died. This indicates that, although effective in the management of nodal metastases, CGD should not be performed on patients with EMPD with a poor prognosis. In such cases, palliative surgery or radiation therapy would be a more appropriate alternative.

The study by Ito et al[12] in the prognostication of EMPD does not analyze the patients according to the number and level (i.e., inguinal vs. pelvic) of nodal disease. Because most of the studies describing SGD did not progress to CGD, there are no available data on this important aspect.[11,13,15] The only other study that described CGD was that by Hegarty et al,[17] who included in their series CGD for two patients who had pelvic nodal disease. One patient underwent neoadjuvant chemotherapy prior to CGD and OS for 40 months, and another underwent adjuvant radiotherapy and had disease-free survival of 13 months. In our series, a patient with pelvic nodal involvement survived for 51 months after pelvic lymphadenectomy without any adjuvant therapy.

Thus, in these patients with pelvic nodal disease, a more thorough metastatic workup including positron emission tomography (PET) would be helpful in avoiding unnecessary surgery. It was shown in a series by Aoyagi et al[24] that although PET was useful in excluding distant metastases in patients with EMPD, it could not reliably detect nodal metastases <10 mm in size.

If the disease is confirmed to be locoregional, based on the favorable survival rates from the aforementioned study and our series, these patients may benefit from neoadjuvant or adjuvant chemoradiotherapy.

**Table 3** Comparison of the series of patients with genital extramammary Paget disease for nodal dissection, regional nodal metastases, and survival.

| Study | No. of patients who underwent lymphadenectomy according to depth of invasion of primary lesion | Sentinel lymph node positivity | Groin inguinal nodal involvement after inguinal lymphadenectomy (inclusive of SLN) | Regional recurrence patterns | Survival analysis of patients with nodal mets | Adjuvant therapy |
|---|---|---|---|---|---|---|
| Tsutsumida et al[11] Japan $n = 36$ | Carcinoma in situ 0/16<br>Microinvasion to papillary dermis 0/6<br>IRD 4/6<br>IST 6/6 | Not done | 3/4 IRD patients positive, (no. of nodes not described)<br>6/6 IST patients positive (no. of nodes not described) | Not described | 5-y cumulative survival rates 33.3% of 6 patients in the IRD group.(range: 19—63 mo)<br>All 3 patients with nodal mets died before 5 y<br>5-y cumulative survival rates 0% in the IST group (range 6—34 mo) | No mention of adjuvant therapy |
| Ito et al[12] Japan $n = 36$ | Intraepidermal 0/18<br>Microdermal invasion 0/9<br>Deep invasion into dermis 5/8 | 4/12 depth of invasion of primary lesion not specified | 2 patients had systemic metes<br>3/3 patients positive (no. of nodes not described) | 2/30 6% local recurrence<br>24-66 mo | 5-y survival of patients with nodal mets 20% | 3 received RT<br>4 received chemotherapy |
| Hatta et al[13] Japan $n = 13$ | Intra epidermal invasion 0/4 | Not done | | | | No mention of adjuvant therapy |
| | Microdermal invasion 0/5 | 1/5 | No inguinal dissection done in the patient with microdermal invasion due to age. | | 18 mo alive with disease | |
| | Dermal invasion 3/4 | 3/4 | 3/3 patients with dermal invasion had positive inguinal nodes<br>(1) 1/10 nodes,<br>(2) 9/9 nodes,<br>(3) 1/8 nodes | Recur at 3 mo<br>Systemic mets <12 mo | (1) 10 mo died of disease<br>(2) 12 mo alive with disease<br>(3) 3 mo no evidence of disease | |
| Zhang et al[15] China $n = 25$ | Intradermal 0/12,<br>Dermal invasion 1/13 | Not done | 1 patient positive (no. of nodes not described) | 7/24 (29.2%), {2/7 nodal mets} (all surgically treated) loco-regional recurrence<br>Median 21 mo | Died 26 mo later with systemic metastases | Not described for the patient with nodal mets |
| Chan et al[16] Hong Kong $n = 48$ | Carcinoma in situ 1/39<br>Dermal invasion 6/9 | Not done | 1 patient had systemic mets<br>6/7 patients positive (no. of nodes not described) | Overall recurrence 14.6%<br>Median 24 mo | No mention about long term survival for all patients | No mention of adjuvant therapy |
| Hegarty et al[17] USA $n = 20$ | Intraepidermal 1/8<br>Dermal invasion 5/10<br>Unknown 2/2 | Not done | 5/5 patients positive (no. of nodes not described) | Not specified | Median survival invasive disease 14.5 mo<br>One disease free 13 mo<br>Two alive with disease 7 and 40 mo<br>Two died 16 and 31 mo | 2 × neoadjuvant chemo 3 × adjuvant chemo |

| | | | | | | |
|---|---|---|---|---|---|---|
| Nakamura et al[18] | *In situ* 0/6 | 0/6 | | | | No mention of adjuvant therapy |
| Japan $n = 27$ | Microinvasion 3/5 | 3/5 | 3/3 patients node positive<br>(1) 1/17<br>(2) 1/11<br>(3) 5/8 | Distant mets | 30 mo<br>37 mo<br>20 mo died | |
| | Dermal invasion 4/16 | 7/16 | 4/4 patients node positive<br>(1) 2/9<br>(2) 1/10<br>(3) 13/13<br>(4) 2/10 | Distant mets<br>Regional and distant mets | 17 mo<br>36 mo<br>9 mo died<br>17 mo alive with disease | |

IRD = invasion reticular dermis; IST = invasion subcutaneous tissue; mets = metastasis; RT = radiotherapy; SLN = sentinel lymph node.

Some centers have explored the use of adjuvant therapy such as chemotherapy or radiotherapy postsurgery. No effective chemotherapy regimen for locally advanced or metastatic EMPD has been established because of the lack of consistent clinical response to any prescribed regimen.[3] In a case described by Takahagi et al,[25] a combination of paclitaxel and trastuzumab was used in a patient with locally recurring skin lesions after initial excision with dramatic clinical response. However, the patient developed cerebral metastases 6 months after successful resolution of the skin lesions.[25] Although encouraging, a consistently effective chemotherapy regimen still needs to be isolated to achieve long-term benefit.

Radiotherapy has been used in the treatment of perianal EMPD with no local recurrence after adjuvant radiotherapy ($n = 0/3$) compared to 25% local recurrence with surgery alone in nine patients.[4] In our case series, none of our patients received adjuvant radiotherapy postsurgery, and there were no patients in whom locoregional recurrence of disease developed.

In the management of early EMPD with no clinical evidence of nodal metastases, some authors have suggested the use of sentinel lymph node (SLN) biopsy.[13] In that study, three of 12 patients with no clinical evidence of nodal involvement were found to have a positive SLN biopsy result and subsequently underwent inguinal lymphadenectomy. This indicates that a significant proportion of patients with no initial clinical evidence of nodal metastases might harbor clinically silent micrometastases. Notably, one patient was found to have extensive nodal involvement in all nine lymph nodes, and subsequent radiological investigations revealed bony metastases. The patient was alive 12 months after surgery.

Patients with EMPD might present with palpable inguinal nodes for a variety of reasons. Enlargement of regional nodes are caused by previous or concurrent infections and inflammation leading to reactive lymphadenopathy or true nodal metastases caused by regional spread of tumor; thus, accurate clinical diagnosis is difficult. Zhang et al[15] reported six cases of palpable inguinal nodes, of which only one patient had metastatic disease. Thus, confirmation of nodal disease with SLN biopsy or imaging can potentially avoid unnecessary nodal dissections.

In a study discussing SLN biopsy in patients with EMPD by Nakamura et al,[18] 10 of 27 patients with genital EMPD were found to have positive SLN biopsy results. There was no postoperative morbidity from the SLN biopsy. Of those 10 patients, seven underwent inguinal nodal dissection. Significantly, four of the seven of those who underwent nodal dissection were disease free during the follow-up period (17—37 months). There was only one patient of 17 with negative SLN in whom inguinal nodal disease eventually developed. Importantly, this study included seven patients with palpable inguinal lymph nodes and no correlation was found between clinically palpable nodes and pathological involvement, three had negative SLN biopsy results, and four had a positive SLN biopsy result. It was thus advocated by the authors that SLN biopsy should be applied in all cases in view of the low morbidity of the procedure and the predictive value of SLN biopsy in inguinal nodal dissection.

In conclusion, primary genital EMPD with nodal metastases historically bears a poor prognosis. However,

aggressive lymphadenectomy in selected cases can provide a long-term survival benefit. The use of Cloquet node in the prediction of pelvic nodal disease should be considered. Based on the literature review, SLN can potentially diagnose occult metastases in otherwise nonenlarged nodes. Further studies to determine the efficacy of SLN in the management of EMPD are needed.

## References


1. Crocker HR. Paget's disease affecting the scrotum and penis. *Trans Pathol Soc Lond*. 1889;40:187—191.
2. Pitman GH, McCarthy JG, Perzin KH, et al. Extramammary Paget's disease. *Plast Reconstr Surg*. 1982;69:238—244.
3. Zollo JD, Zeitouni NC. The Roswell Park Cancer Institute experience with extramammary Paget's disease. *Br J Dermatol*. 2000;142, 59—42.
4. Besa P, Rich TA, Delclos L, et al. Extramammary Paget's disease of the perineal skin: role of radiotherapy. *Int J Radiat Oncol Biol Phys*. 1992;24:73—78.
5. Barnhill RL. *Textbook of Dermatopathology*. 2nd ed. New York, NY: McGraw-Hill Companies; 2004:770—772.
6. Ohnishi T, Watanabe S. The use of cytokeratins 7 and 20 in the diagnosis of primary and secondary extramammary Paget's disease. *Br J Dermatol*. 2000;142:243—247.
7. Werling RW, Yaziji H, Bacchi CE, Gown AM. CDX2, a highly sensitive and specific marker of adenocarcinomas of intestinal origin: an immunohistochemical survey of 476 primary and metastatic carcinomas. *Am J Surg Pathol*. 2003;27:303—310.
8. Weedon D. *Skin Pathology*. 2nd ed. New York, NY: Churchill Livingstone; 2002:883—884.
9. Kodama S, Kaneko T, Saito M, Yoshiya N, Honma S, Tanaka K. A clinicopathologic study of 30 patients with Paget's disease of the vulva. *Gynecol Oncol*. 1995;56:63—70.
10. Parker LP, Parker JR, Bodurka-Bevers D, et al. Paget's disease of the vulva: pathology, pattern involvement, and prognosis. *Gynecol Oncol*. 2000;77:183—189.
11. Tsutsumida A, Yamamoto Y, Minakawa H, Yoshida T, Kokubu I, Sugihara T. Indications for lymph node dissection in the treatment of extramammary Paget's disease. *Dermatol Surg*. 2003;29:21—24.
12. Ito Y, Igawa S, Ohishi Y, Uehara J, Yamamoto AI, Iizuka H. Prognostic indicators in 35 patients with extramammary Paget's disease. *Dermatol Surg*. 2012;38:1938—1944.
13. Hatta N, Morita R, Yamada M, et al. Sentinel lymph node biopsy in patients with extramammary Paget's disease. *Dermatol Surg*. 2004;30:1329—1334.
14. Karakousis CP, Driscoll DL. Positive deep node in the groin and survival in malignant melanoma. *Am J Surg*. 1996;171:421—422.
15. Zhang N, Gong K, Zhang X, Yang Y, Na Y. Extramammary Paget's disease of scrotum—report of 25 cases and literature review. *Urol Oncol*. 2010;28:28—33.
16. Chan JY, Li GK, Chung JH, Chow VL. Extramammary Paget's disease: 20 years of experience in Chinese population. *Int J Surg Oncol*. 2012;2012:416418.
17. Hegarty PK, Suh J, Fisher MB, et al. Penoscrotal extramammary Paget's disease: the University of Texas M. D. Anderson Cancer Center contemporary experience. *J Urol*. 2011;186:97—102.
18. Nakamura Y, Fujisawa Y, Ishikawa M, et al. Usefulness of sentinel lymph node biopsy for extramammary Paget disease. *Br J Dermatol*. 2012;167:954—956.
19. Jabbar AS. Perianal extramammary Paget's disease. *Eur J Surg Oncol*. 2000;26:612—614.
20. Yoshino K, Yamazaki N, Yamamoto A, et al. Lymph node metastases and sentinel lymph node biopsy in extramammary Paget's disease. *Jpn J Dermatol*. 2006;116:1473—1477.
21. Shen P, Conforti AM, Essner R, Cochran AJ, Turner RR, Morton DL. Is the node of Cloquet the sentinel node for the iliac/obturator node group? *Cancer J*. 2000;6:93—97.
22. Essner R, Scheri R, Kavanagh M, Torisu-Itakura H, Wanek LA, Morton DL. Surgical management of the groin lymph nodes in melanoma in the era of sentinel lymph node dissection. *Arch Surg*. 2006;141:877—882.
23. Koh YX, Chok AY, Zheng H, Xu S, Teo MC. Cloquet's node trumps imaging modalities in the prediction of pelvic nodal involvement in patients with lower limb melanomas in Asian patients with palpable groin nodes. *Eur J Surg Oncol*. 2014;40:1263—1270.
24. Aoyagi S, Sato-Matsumura KC, Shimizu H. Staging and assessment of lymph node involvement by 18F-fluorodeoxyglucose-positron emission tomography in invasive extramammary Paget's disease. *Dermatol Surg*. 2005;31:595—598.
25. Takahagi S, Noda H, Kamegashira A, et al. Metastatic extramammary Paget's disease treated with paclitaxel and trastuzumab combination chemotherapy. *J Dermatol*. 2009;36:457—461.